Andrx
CORPORATION

3316 '00 JAN -6 P3:19

October 22, 1999

Janet Woodcock, MD
Director, Center for Drug Evaluation
and Research
Food and Drug Administration
Rockville, MD 20857

Re: Docket No. 98P-0145

Dear Dr. Woodcock:

This is in response to your letter of today's date, addressed to Dr. Chen, responding to the referenced Citizen's Petition we filed on February 26, 1998 and the supplement thereof filed September 9, 1998. While we have not had the opportunity to fully consider the comments in your letter, the following was immediately evident:

- The Andrx ANDA data referred to in page 8 of your letter was for our Dilacor XR® submission (ANDA 74-852), and not our ANDA for a bioequivalent version of Cardizem® CD (ANDA 74-752).

- Your letter appears to place the burden of establishing medical significance on persons other than the ANDA applicant, which is contrary to your regulation, and may be impossible to obtain due to the unavailability of the ANDA product for testing purposes. As a result, our July 15, 1998 letter to your office (referencing the Citizen Petition) stated that Andrx would provide a supply of our Cardizem CD product and even underwrite the cost to perform the tests requested by your response. Andrx remains willing to undertake this commitment.

- Your letter on page 10 and 11 invites Andrx or others to submit additional data that establishes the medical significance of the matters discussed in our Citizen Petition. While Andrx has already provided this test data, there is no mention of that data in your letter. Specifically, our September 15, 1999 letter (referencing the Citizen Petition), a copy of which is attached, referred to a study performed by or for Forest Laboratories — Biovail's licensee for its Tiazac® product — establishing that significance. Moreover, we today received a copy of the October 1999 edition of the American Journal of Hypertension that elaborates upon that test data and again concludes that the study demonstrates a "close dependency of the hemodynamic effects of

98P-0145 LET 2

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diltiazem on its plasma concentration" and "identifies pharmacokinetic and clinical disparities produced by different formulations of this hypertensive agent" (copy attached). Lastly, the October 1, 1999 letter from Robert W. Piepho, Ph.D., of the University of Missouri – Kansas City School of Pharmacy that refers to yet additional test data on this subject (copy attached). With the exception of the article, the data requested by your letter was already submitted. Yet, there was no reference or apparent consideration given to this data by FDA[1].

As we believe there were a significant amount of material errors or omissions involved with the formulation of your response, we request FDA's immediate attention to and reconsideration of this matter.

Sincerely,

Scott Lodin
Vice President and General Counsel

[1] We also note the apparent ethical and possibly legal problems arising out of the fact that Andrx was required to provide test data which Biovail must have known about, yet failed to disclose to FDA concerning this matter.

Andrx
PHARMACEUTICALS, INC.

September 15, 1999

Dr. Janet Woodcock, Director
Center for Drug Evaluation and Research
Food and Drug Administration
Document Management Branch (HFA-305)
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

RE: Citizen Petition Docket Number 98-0145

Dear Dr. Woodcock:

FDA is still reviewing and analyzing the issues raised by the referenced Citizen Petition that Andrx Pharmaceuticals, Inc. ("Andrx") filed on February 26, 1998 (the "Petition"). The Petition reflects Andrx' position that, where a reference listed drug manifests a distinct and controlled two-peak pharmacokinetic profile and there is a correlation between that profile and the observed pharmacodynamic effect, a potential ANDA product should manifest a similar PK/PD correlation. If the ANDA product fails to match that pharmacokinetic profile, it is the ANDA sponsor's responsibility to provide data that establishes that (i) the failure to match the two-peak profile is intentional, (ii) such match is not essential to safe and effective use of the drug, and (iii) such a match is medically insignificant to generic substitution for the reference drug product. See 54 Fed. Reg. at 28882 (1989).

To further clarify some of the issues involved, attached hereto as Exhibit A is a summary of a scientific study that clearly refutes certain comments filed in response to the Petition (the "Study"). The results of this Study, while only recently discovered by Andrx, were presented at the American Society of Hypertension, Twelfth Scientific Meeting Exposition, May 27-31, 1997, in San Francisco, California and, as evidenced by the press release attached hereto as Exhibit B, was used by Forest Laboratories, Inc. ("Forest") in the marketing of Tiazac®, an extended release diltiazem product manufactured by Biovail Corporation International ("Biovail").

The stated objective of the Study was "to determine [whether the] pharmacokinetic differences [between Tiazac® and Cardizem® CD, two extended release diltiazem drugs] resulted in appreciable pharmacodynamic differences." The Study concludes as follows:

> "These data demonstrate that administering the same dose of diltiazem with different release systems and pharmacokinetic profiles results in corresponding clinically important pharmacodynamic differences. The Tiazac release system produced greater and more consistent blood pressure reduction over the 24-hour monitoring period than occurred with Cardizem® CD." (emphasis added).

The Study clearly supports Andrx' argument – and the Petition – that (1) a specific discernable PK/PD correlation exists for Cardizem® CD, and (2) this correlation is "clinically important"[1]. The Study also contradicts the arguments of Biovail and others who opposed the Petition that the pharmacodynamic effect observed for Cardizem® CD is meaningless or not clinically significant.

Tiazac®, Cardizem® CD, Dilacor® XR and various other products FDA has previously approved as bioequivalent versions of Cardizem® CD and Dilacor® XR, are all extended release diltiazem products that are presently (or soon will be) marketed in the US[2]. Forest chose to promote the significance of the Study and its conclusions as part of its effort to position Tiazac®, which it licensed from Biovail, vis-a-vis Cardizem® CD in that marketplace. In contrast, Biovail submitted positions in opposition to the Petition without ever referring to the Study. Since the Study provides compelling clinical evidence refuting Biovail's positions in opposition to the Petition, we view Biovail's opposition papers as highly suspect[3].

CONCLUSION:

For all of the reasons previously set forth in the Petition and in Andrx' responses dated September 9, 1998 (Docket C-7), September 16, 1998 (Docket C-7A) and July 15, 1999 (Docket C-14), Andrx requests that FDA clarify the bioequivalence guidance and withhold approval of any pending and future ANDAs, unless the ANDA sponsor makes the necessary substantiating demonstrations.

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1 Andrx has not received a copy of the complete Study, and therefore can not express any thoughts on its additional conclusion that "the Tiazac release system produced greater and more consistent blood pressure reduction over the 24-hour monitoring period than occurred with Cardizem® CD."

2 On January 26, 1998, the FDA Director, Division of Cardio-Renal Drug Products, issued a memorandum referring to the clinical data that established some of these and other diltiazem products to be safe and efficacious (the criteria for an NDA approval), but states that this data is not sufficient to allow them to be approved as bioequivalent to Cardizem ® CD. Exhibit C.

3 Instead, Biovail has essentially argued that it is the responsibility of Andrx, and not the ANDA sponsor, to provide additional data that supports the positions set forth in the Petition.

In the case of Cardizem® CD, for all of the medical reasons set forth in the letters from Drs. White, Pitt, Jusko and Solomon (Dockets C-1, C-2, C-9 and C-11), Andrx requests that FDA withhold approval of any pending and future ANDAs that do not demonstrate matching two-peak pharmacokinetic profiles unless the ANDA applicant demonstrates, through clinical data, that there are no significant medical differences between its product and the reference drug.

Respectfully submitted,

Scott Lodin
Vice President & General Counsel
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314
(954) 584-0300

cc: Douglas L. Sporn,
Director, Office of Generic Drugs
Roger Williams, M.D.
Deputy Center Director, Office of Pharmaceutical Science

Comparison of the Pharmacodynamic Profiles of Two Different Long-Acting Diltiazem Delivery Systems

David H.G. Smith, M.D. and Joel M. Neutel, M.D.
Orange County Heart Institute and Research Center, Orange, CA and
Clinical Investigation Analysis, Orange, CA

Presented at the American Society of Hypertension, Twelfth Scientific Meeting Exposition, May 27-31, 1997, San Francisco, CA.

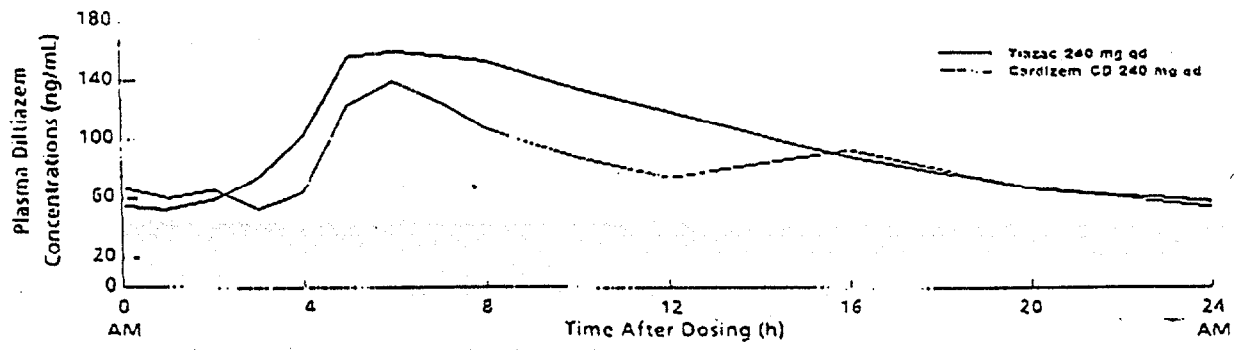
INTRODUCTION

To attain effective blood pressure control with once-daily dosing, inherently short-acting drugs such as the calcium channel blockers rely on a variety of extended release drug delivery systems. In the case of diltiazem, Tiazac® uses a single microbead diltiazem population while Cardizem® CD uses two microbead diltiazem populations to attain 24-hour blood pressure control. The pharmacokinetic profiles resulting from these two delivery systems have previously been shown to be different (see below) mainly through the 10-16th hour post-dosing period with maximum differences occurring at the midpoint of the 24-hour dosing cycle.

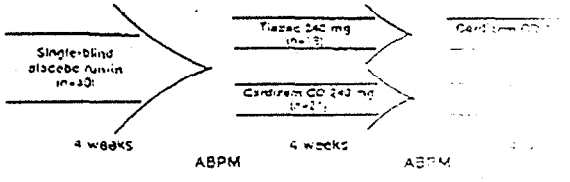
OBJECTIVE

To determine if these pharmacokinetic differences resulted in appreciable pharmacodynamic differences, we conducted a double-blind, randomized, crossover study comparing the ambulatory blood pressure profiles in mild-to-moderate hypertensive patients receiving Tiazac 240 mg and Cardizem CD 240 mg .

Pharmacokinetic Profiles of Tiazac and Cardizem CD



treatment sequence was Tiazac followed
(see below). Dosing took place at 8.00 a.m.
and all patients were subjected to ambulatory
pressure monitoring at the end of the placebo
and at the end of each of the four-week treatment



...atory blood pressure significantly.

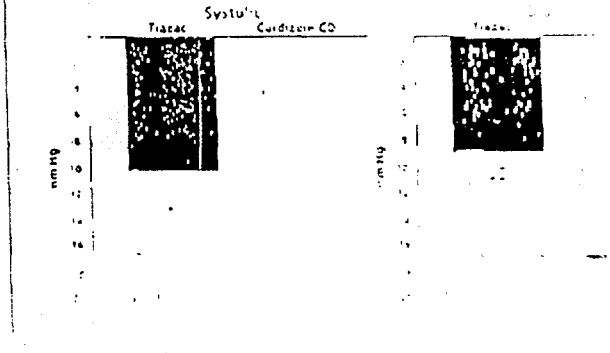
24-Hour Ambulatory Blood Pressure Mean

	Baseline	Tiazac	Cardizem CD
Systolic BP	151.7 ±12.23	144.53 ±11.97*	
Diastolic BP	95.3 ± 8.01	89.12 ± 8.04*	
Heart Rate	76.03 ± 12.09	76.55 ±12.28	

*p < 0.01 vs baseline

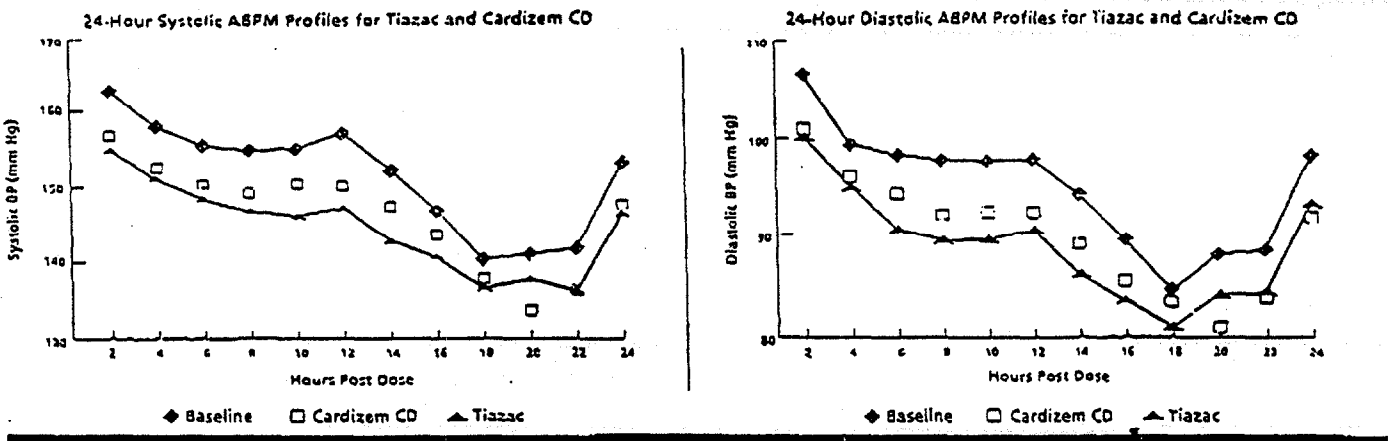
...pharmacokinetic profiles are different, Tiazac resulted in statistically ...re than Cardizem CD. Similarly, Tiazac resulted in greater reductions ...g period (i.e., 12-13 hours after dosing) when pharmacokinetic ... ...ficant greater reductions in both systolic and diastolic blood pres...

ABPM Blood Pressure Reductions During the Midpoint of the Dosing Period



RESULTS

24-hour ambulatory blood pressure monitoring profiles for both systolic and diastolic blood pressure while taking Tiazac and Cardizem CD are illustrated below. For most of the 24-hour dosing interval, blood pressure levels were lower with the Tiazac preparation.



Blood Pressure and Heart Rate for Various Components of the 24-Hour Monitoring Period are Tabulated Below

Systolic Blood Pressure	Baseline	Tiazac	Cardizem CD	Tiazac vs Cardizem CD *p* Value
10-16th hours post dose	152.703 ± 15.2258	143.945 ± 13.6193	147.588 ± 12.4083	*
Midpoint of dosing period	154.278 ± 17.0050	143.624 ± 16.4525	149.034 ± 13.1027	*
Last 4 hours of dosing period	147.404 ± 15.1227	141.176 ± 12.2491	141.605 ± 14.7116	NS
Daytime means	157.834 ± 10.7116	149.875 ± 11.6571	152.265 ± 10.7553	NS
Nighttime means	148.041 ± 14.2014	141.250 ± 13.3023	142.813 ± 12.8740	NS

Diastolic Blood Pressure	Baseline	Tiazac	Cardizem CD	Tiazac vs Cardizem CD *p* Value
10-16th hours post dose	94.5039 ± 10.4287	87.2493 ± 8.1424	89.6183 ± 9.2471	**
Midpoint of dosing period	95.5000 ± 11.3378	86.5385 ± 9.7468	91.0684 ± 9.9763	***
Last 4 hours of dosing period	93.7941 ± 10.2667	89.1424 ± 11.5250	88.0889 ± 9.8657	NS
Daytime means	100.500 ± 7.37652	93.5740 ± 8.58860	95.7490 ± 8.43965	NS
Nighttime means	92.1323 ± 9.21514	86.4095 ± 8.53639	87.2512 ± 8.47764	NS

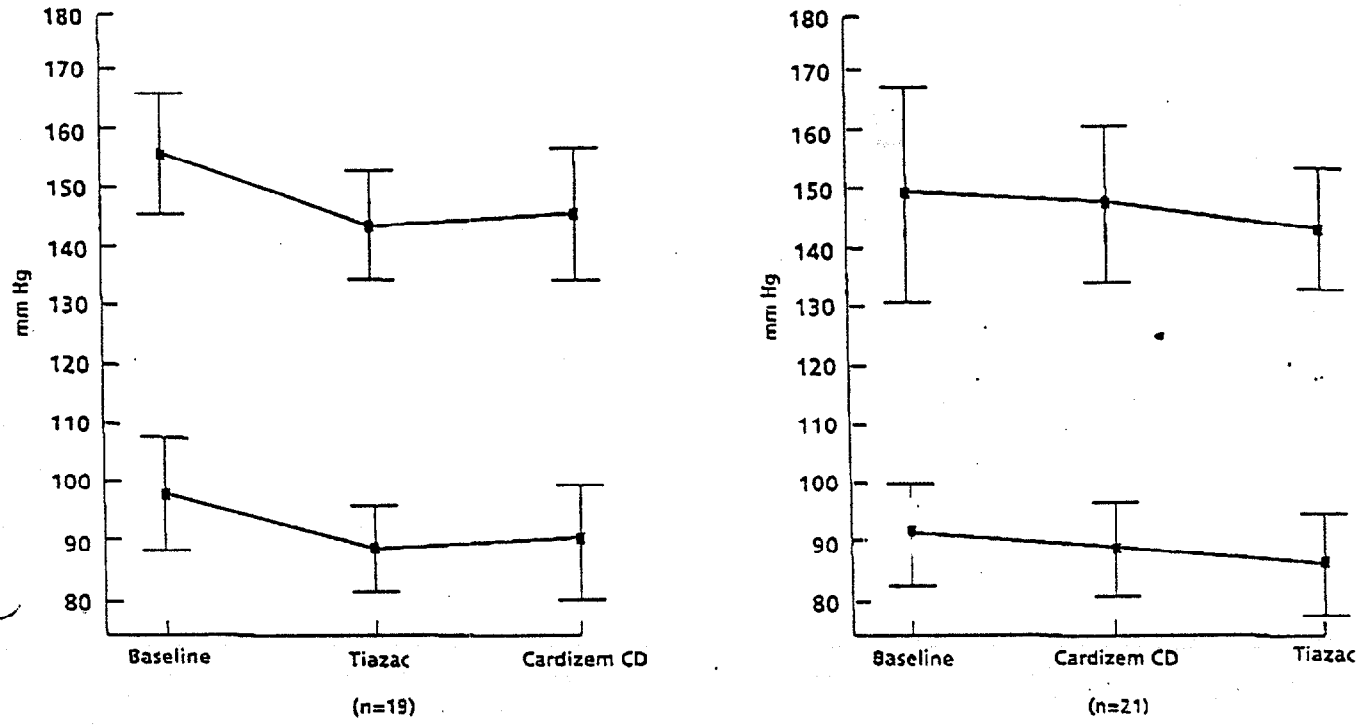
Heart Rate	Baseline	Tiazac	Cardizem CD	Tiazac vs Cardizem CD *p* Value
10-16th hours post dose	80.6024 ± 13.3360	78.2746 ± 14.1155	78.6234 ± 13.3937	NS
Midpoint of dosing period	81.2927 ± 13.8937	78.4464 ± 14.8951	78.7479 ± 12.5158	NS
Last 4 hours of dosing period	77.7592 ± 11.0650	76.4604 ± 10.3236	77.5010 ± 12.4180	NS
Daytime means	82.2283 ± 13.3905	81.1012 ± 14.0522	80.9080 ± 13.7514	NS
Nighttime means	75.4808 ± 11.5801	73.7908 ± 11.6869	74.0076 ± 11.7444	NS

* p < 0.05 ** p < 0.01 *** p < 0.001
NS = Not statistically significant

RESULTS

The treatment sequence changing from Tiazac to Cardizem CD resulted in a 2.6 mm Hg increase in systolic blood pressure and a 2.1 mm Hg increase in diastolic blood pressure. Changing from Cardizem CD to Tiazac resulted in an additional decrease of 4.5 mm Hg in systolic blood pressure and a 2.6 mm Hg decrease in diastolic blood pressure.

Effect of Treatment Sequences on Blood Pressure During the 10–16th Hour Post-Dose Period



The pharmacodynamic differences in this study were not associated with any episodes of hypotension, differences in adverse effects, or heart rate profiles.

CONCLUSIONS

These data demonstrate that administering the same dose of diltiazem with different release systems and pharmacokinetic profiles results in corresponding clinically important pharmacodynamic differences. The Tiazac release system produced greater and more consistent blood pressure reduction over the 24-hour monitoring period than occurred with Cardizem CD

EXHIBIT B

Once-daily

TIAZAC™

(diltiazem HCl)

extended-release capsules

[FOREST LABORATORIES BACKGROUNDER] NOVEL EXTENDED-RELEASE DILTIAZEM CONTROLS BLOOD PRESSURE OVER 24 HOURS WITH AN EXCELLENT SAFETY PROFILE

FOREST LABORATORIES BACKGROUNDER

Forest Pharmaceuticals, a subsidiary of Forest Laboratories, Inc., is an international health care company that develops, manufactures and distributes both branded and generic forms of prescription drug products as well as nonprescription pharmaceuticals sold over-the-counter to treat a wide range of illnesses.

Forest, publicly traded on the American Stock Exchange (ASE: FRX), markets products principally in the United States, in western and eastern Europe, and in Puerto Rico and other Caribbean islands.

Forest markets a broad range of human prescription pharmaceutical products, including Aerobid®, Lorcet® 10/650, Lorcet® Plus, Flumadine®, Levothroid®, Tessalon®, Esgic-plus, AeroChamber®, Cervidil and Tiazac among others.

NOVEL EXTENDED-RELEASE DILTIAZEM CONTROLS BLOOD PRESSURE OVER 24 HOURS WITH AN EXCELLENT SAFETY PROFILE

Widest Range of Single-Capsule, Extended-Release Dosing Options Available

NEW YORK -- February 9, 1996 -- A novel formulation of diltiazem hydrochloride (TIAZAC)[1] for hypertension is now available from Forest Laboratories, Inc. The new, once-daily calcium channel blocker effectively reduces blood pressure of hypertensive patients over the 24-hour dosing interval with a side-effect profile comparable to placebo, even when dosed up to 360 mg.

Blood pressure normally varies throughout the day and night and is influenced by the patient's own circadian rhythm and external stimuli. In hypertensive patients, blood pressure needs 24-hour control to achieve blood pressure levels that approach treatment goals[2].

Through its unique extended-release, osmotic-driven diffusion system of concentrated diltiazem beads, TIAZAC delivers smooth 24-hour plasma levels, which are highly correlated with blood pressure measurements. When properly dosed, TIAZAC provides smooth and predictable 24-hour blood pressure control. A greater blood pressure reduction is achieved with TIAZAC when blood pressure is at its highest, yet TIAZAC achieves blood pressure reduction without causing hypotension during periods of lower blood pressure.

"TIAZAC provided a dose-related diastolic and systolic blood pressure reduction at each dosage level," added Gosse Bruinsma, MD, Medical Director at Forest Laboratories. "In a dose-escalation trial, seven out of ten patients responded to TIAZAC monotherapy when dosed up to 540 mg."

In clinical studies, doses of TIAZAC up to 360 mg exhibited a side-effect profile similar to that of the lower doses, and similar to placebo. Moreover, TIAZAC can be safely dosed up to 540 mg. In

clinical trials, absorption of TIAZAC was not affected by food intake: TIAZAC can be taken with or without food, even high-fat meals.

"The drug delivers a consistent level of diltiazem well within the therapeutic plasma range, as evidenced by the effective 24-hour blood pressure control that diltiazem achieves," added Joel Neutel, MD, Assistant Professor of Medicine and Head of the Hypertension Research Center at the University of California at Irvine.

TIAZAC, a highly concentrated formulation of diltiazem, enables more drug to be contained inside a smaller capsule. This unique formulation allows for both smaller capsules for a given dosage, relative to the same dose of other once-daily diltiazem products, and for five dosage strengths: 120, 180, 240, 300 and 360 mg. This means that TIAZAC offers physicians the widest range of available single-capsule dosages among once-daily diltiazems, allowing for maximum dosing flexibility with once-daily therapy.

TIAZAC offers a significant savings in monthly treatment costs when compared to other leading calcium channel blockers. At the most-prescribed, extended-release diltiazem dose level (180 mg), TIAZAC costs $27.84 for one month's therapy[3] compared with Cardizem® CD at $37.00 and Dilacor XR® at $32.72.

In clinical trials, TIAZAC showed no clinically significant changes in ECG readings, no increases in 2nd- or 3rd-degree AV heart block and no more than a slight decrease in heart rate. TIAZAC was well tolerated in clinical trials. No reflex tachycardia is associated with chronic use. The most commonly reported side effects were headache, peripheral edema, pain, dizziness and asthenia. First-degree AV-block has been reported infrequently (less than 1%) in clinical trials with other diltiazem products.

In a major comparative trial of single-drug therapy for hypertension, diltiazem showed blood pressure control greater than or comparable to that of six other antihypertensives from different drug classes. African-American patients in the study responded especially well to diltiazem therapy, while Caucasians responded well to all drug classes (except for a lower efficacy shown with hydrochlorothiazide in younger whites).

TIAZAC, as with all diltiazem formulations, should not be used in patients with severe hypotension (less than 90 mm Hg systolic), patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission, patients with sick sinus syndrome or 2nd-/3rd-degree AV block (unless used with a functioning ventricular pacemaker) and patients who have demonstrated hypersensitivity to the drug. This drug should be used with caution in patients with impaired kidney, liver or heart function.

Forest Pharmaceuticals, a subsidiary of Forest Laboratories, Inc., is an international health care company that develops, manufactures and distributes both branded and generic forms of prescription drug products as well as nonprescription pharmaceuticals sold over-the-counter to treat a wide range of illnesses. Forest is publicly traded on the American Stock Exchange (ASE: FRX).

1. Full prescribing information enclosed.
2. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md: National Heart, Lung, and Blood Institute; 1994. US Department of Health and Human Services publication NIH 93-1088.
3. Monthly costs determined from January 1996 Drug Topics® Red Book® average wholesale prices (AWP) of TIAZAC, Cardizem® CD and Dilacor XR® in 90-count bottles.
   AWP does not necessarily reflect actual prices paid by consumers or pharmacies.
   Price comparisons are not intended to imply similar levels of effectiveness.
   TIAZAC, Cardizem® CD and Dilacor XR® are BC rated. Bioequivalence between these products has not been demonstrated.

When switching brands of drugs, additional costs may be incurred for office visits or monitoring.

Return to Tiazac home page.

Exhibit C

JAN 30 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION Public Health Service

Memorandum

DATE : January 26. 1998

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110. Lipicky

SUBJECT: NDA 20-401/S-007, Controlled Release Diltiazem, Tiazac, Biovail

TO : NDA File

Introduction

Diltiazem is well known to be antihypertensive and antianginal in man (here by well known I mean through dozens of publications in reputable, peer-reviewed medical journals as well as through having four other NDAs approved for the use of diltiazem as an antianginal, or as an antihypertensive, or for both indications, or for the treatment of supraventricular arrhythmias, each approval supported by clinical trials). The approved NDAs are:

1) NDA 18-602, Immediate Release Diltiazem, **Cardizem**, approved only for angina, Marion Merrell Dow, taken orally three-times-a-day, patent expired,
2) NDA 19-471, Controlled Release Diltiazem, **Cardizem SR**, approved only for hypertension, Marion Merrell Dow, taken orally twice-a-day, patent expires Jan. 26, 2005,
3) NDA 20-027, Intravenous Diltiazem, **Cardizem Injection**, approved only for paroxysmal supraventricular tachycardia and paroxysmal atrial flutter/fibrillation, Marion Merrell Dow, Intravenous,
4) NDA 20-062, Controlled Release Diltiazem, **Cardizem CD**, approved for angina and hypertension, Marion Merrell Dow, taken orally once-a-day, patent expires Jan. 16, 2007 & Mar. 26, 2008,
5) NDA 20-092, Controlled Release Diltiazem, **Dilacor XR**, approved only for hypertension, Rhone-Poulenc Rorer Pharmaceuticals, Inc, taken orally once-a-day, patent expires June 14, 2006.
6) NDA 20-401, Controlled Release Diltiazem,. **Tiazac**, approved for hypertension, taken orally, once-a-day. Biovail Corporation International. Patent holder Galephar P.R., Inc. Ltd., expires June 25, 2013. **Tiazac** was also approved in the United Kingdom in February, 1996 under the trade name **Viazem SR**.

Bolded names are **Trade Names** for the formulations of diltiazem.

NDAs 1 though 5 were full NDAs [505(b)(1)] in that they were supported by chronic animal toxicology and animal reproduction studies, as well as manufacturing & controls, in addition to the clinical trials that were requisite for approval. The 4 Marion Merrell Dow NDAs were supported by the original animal toxicology & reproduction data that were submitted with NDA 18-602. The Rhone-Poulenc Rorer NDA was supported by chronic animal toxicology & reproduction studies conducted by [redacted] (in support of an immediate release formulation which [redacted] never got to market), by right to reference.

Hoechst-Roussel developed another controlled release formulation of diltiazem (the product submitted as NDA 20-401, **Tiazac**) that was intended to control blood-pressure suitably when taken once-a-day. NDA 20-401 (the Hoechst-Roussel Pharmaceuticals NDA) and contained the results of studies that clearly demonstrate that **Tiazac** is <u>not bioequivalent</u> with immediate release diltiazem, **Cardizem CD** nor **Dilacor XR** (consequently, although not part of the empirical data, **Tiazac** would also not be bioequivalent to **Cardizem SR** and **Cardizem Injection**). Therefore **Tiazac** could not be approved as an ANDA (e.g., 505(j)), since it was known that it is bioinequivalent to any of the approved formulations of diltiazem.

NDA 20-401 was approved in September 1995 as a 505(b)(2) NDA on the basis of clinical trials that involved 281 patients or normal volunteers (133 volunteers to characterize the biopharmaceutical properties of their formulation [8 studies] and 148 patients with hypertension that were randomized to one of two placebo controlled, dose-ranging trials). In December 1995, Biovail obtained a right of reference for the pharmacology/toxicology data from Hoechst Marion Roussel, so NDA 20-401 was converted to a 505(b)(1) NDA. This right of reference supports NDA 20-401 and any NDAs or supplemental NDAs containing the diltiazem formulation that was originally submitted to NDA 20-401.

Biovail Corporation International acquired the manufacturing site (previously know as Galephar P.R., Inc. LTd. Galephar, the owner of the patent for this formulation), now called Biovail Laboratories, and transferred the ownership of the NDA to them. Biovail Laboratories manufactures Tiazac, and Forest Pharmaceuticals will be the distributor. Tiazac is currently listed in the 1998 PDR under Forest Pharmaceuticals name.

The applicant has submitted a 6 week randomized, double-blind, placebo-controlled, parallel-group, dose-ranging clinical trial. This trial randomized 257 subjects to one of 5 arms, placebo, 120 mg, 240 mg, 360 mg, or 540 mg of Tiazac, once-a-day. The primary endpoint was the duration of symptom limited exercise at trough, ST segment depression was also evaluated, diaries for counting angina attacks were kept and nitroglycerine consumption was recorded. The NDA supplement contained a full study report and an electronic data base that contained all variable recorded on case report forms.

The placebo subtracted increases in exercise time were 12, 27, 19 and 18 seconds for the 120 mg, 240 mg., 360 mg., and 540 mg dosage groups, respectively. More details can be found in the reviews conducted by Dr. U (completed October, 1997) and Dr. Karkowsky (also completed in October, 1997).

Further details relevant to NDA 20-401 related to the formulation can be found in my previous memoranda. NDA 20-401/S-007 is approvable for use in angina.

cc: NDA 20-401
HFD-110
HFD-110/DRoeder

VOLUME 12, NUMBER 10, PART 1, OCTOBER 1999

American Journal of Hypertension

JOURNAL OF THE AMERICAN SOCIETY OF HYPERTENSION

CONTENTS

ORIGINAL CONTRIBUTIONS

AMERICAN JOURNAL OF HYPERTENSION (ISSN 0895-7061) is issued monthly by Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in the United States at 3575 Hempland Rd., Lancaster, PA. Subscription prices per year: For Customers in the USA only: Institutional Rate: US $320.00, Personal Rate: US $175.00, Student/Resident Rate: US $95.00. For Surface Mail Delivery to Customers in Europe, CIS, and Japan: Institutional Rate: NLG 723.00, Personal Rate: NLG 437.00, Student/Resident Rate: NLG 280.00. For Surface Airlift to Customers in Europe: Institutional Rate: NLG 784.00, Personal Rate: NLG 498.00, Student/Resident Rate: NLG 341.00. For Surface Airlift to Customers in Japan: Institutional Rate: NLG 828.00, Personal Rate: NLG 542.00, Student/Resident Rate: NLG 384.00. For Surface Mail Delivery to Customers in all other Countries: Institutional Rate: US $367.00, Personal Rate: US $222.00, Student/Resident Rate: US $142.00. Prices include postage as specified and are subject to change without notice. For additional information contact Elsevier Science Customer Support Department, P.O. Box 945, New York, NY 10010, Tel.: (212) 633-3730. Toll Free (for customers in North America) 1-888-4ES-INFO, Fax: (212) 633-3680, E-mail: usinfo-f@elsevier.com. Periodicals postage paid at New York, NY, and at additional mailing offices. POSTMASTER: Send address changes to AMERICAN JOURNAL OF HYPERTENSION, Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010.

CONTENTS *continued*

BRIEF COMMUNICATIONS

AJH 1999;12:1030–1037

Comparisons of the Effects of Different Long-Acting Delivery Systems on the Pharmacokinetics and Pharmacodynamics of Diltiazem

David H.G. Smith, Joel M. Neutel, and Michael A. Weber

The benzothiazepine calcium channel antagonist diltiazem is a short-acting drug. To achieve effective 24-h blood pressure control with once-daily dosing, it relies on various extended drug-delivery systems that have grown in importance as a result of the recent reports relating the use of short-acting calcium channel antagonists to increased cardiovascular morbidity. This study examines the pharmacokinetics and resulting pharmacodynamics of two different delivery systems, each loaded with 240 mg of diltiazem and administered to 40 moderately hypertensive patients in a randomized, double-blind crossover trial. After a 4-week, single-blind placebo lead-in, patients with a clinical diastolic blood pressure of ≥100 mm Hg were randomized to either the single or dual microbead diltiazem delivery system for a 4-week period. At the end of this period, each subject was evaluated with 24-h ambulatory blood pressure monitoring and subjected to 24-h inpatient pharmacokinetic analysis on separate days. This was followed by a similar 4-week period in which each subject was treated with the alternative delivery system.

For diltiazem, the area under the curve for plasma concentration versus time and the maximum plasma concentration attained by the single microbead system exceeded the values achieved by the dual bead system by 15% and 25%, respectively. These differences were greatest from the 3rd through the 13th h after dosing. During this period, both systolic and diastolic ambulatory blood pressure was significantly lower when the single microbead system was used. When compared with baseline blood pressure, blood pressure reductions achieved with the single microbead system exceeded reductions achieved with the dual microbead system by at least 2 mm Hg for 10 of the 24 postdose hours. Heart rates were slightly reduced but not significantly different. This improved blood pressure control at higher plasma levels of diltiazem suggests that a more efficient delivery system could provide better blood pressure control for identical doses of diltiazem. Am J Hypertens 1999;12:1030–1037

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Diltiazem hydrochlorothiazide is a benzothiazepine calcium channel antagonist with proved antianginal and antihypertensive efficacy.[1,2] Like most calcium channel antagonists, it is a short-acting compound and relies on a variety of slow-release delivery systems to increase its duration of action and thereby decrease the dosing frequency.[3] This role for delivery systems has become increasingly important in view of recent reports linking the use of short-acting calcium channel antagonists to increased cardiovascular morbidity and mortality.[4–6] Furthermore, the tendency of adverse cardiovascular events to cluster in the early morning hours in association with the circadian blood pressure surge underscores the need for effective slow-release drug delivery systems that maintain their antihypertensive effects throughout the dosing interval.[7]

Three separate once-daily formulations of diltiazem are approved for use by the US Food and Drug Administration (FDA) in the treatment of hypertension in the US.[8] In chronological order of approval they are the following: Cardizem CD (Hoechst Marion Roussel, Inc., Kansas City, MO), Dilacor XR (Watson Laboratories Inc., Corona, CA), and Tiazac (Forest Pharmaceuticals, Inc., St. Louis, MO). Cardizem CD uses a dual population of microbeads (dual microbead system) enclosed within a single capsule.[9,10] The two populations of microbeads differ only in the thickness of a copolymer that surrounds them and controls the release of diltiazem. Those with a thin coating release 40% of the total diltiazem in the first 12 h, whereas those with the thick coating release the remaining diltiazem during the second 12 h. Thus, there are two phases to the release of diltiazem. In contrast, Tiazac uses a single population of microbeads (single microbead system) with a uniform copolymer coating.[11,12] This allows for the release of diltiazem in one phase over a 24-h period. Dilacor XR uses a series of Geomatrix tablets, each containing 60 mg of diltiazem enclosed within a single capsule.[13] Release of diltiazem is controlled by different hydration rates for the faster-hydrating inner core that is surrounded by a slower-hydrating outer core. A recent trial comparing the pharmacokinetics of these three delivery systems in normal individuals has demonstrated that the single microbead system provides 24% more diltiazem than the dual microbead system and 29% more diltiazem than the geomatrix system when these systems are loaded with identical doses of diltiazem.[11]

Despite the crucial role of delivery systems in imparting many desirable features of effective once-daily antihypertensive agents to intrinsically short-acting calcium antagonists, clinical trials comparing their ability to deliver antihypertensive agents to hypertensive patients have rarely been reported. Furthermore, because studies with diltiazem show increased blood pressure reduction with increasing plasma drug concentrations,[14] it is of interest to determine if the pharmacokinetic differences in different delivery systems translate into pharmacodynamic differences. In this randomized crossover clinical trial, we compared the pharmacokinetic and pharmacodynamic effects of 240-mg doses of diltiazem delivered alternately by the single and dual microbead systems to 40 moderately hypertensive patients. We have shown that the single microbead system differs from the dual microbead system in delivering diltiazem and that this translates into differing effects on the 24-h ambulatory blood pressure profiles.

METHODS

This two-site study was conducted at the clinical research facilities of the Orange County Heart Institute and Research Center, Orange, CA, and Memorial Research Medical Clinic, Long Beach, CA, in compliance with FDA guidelines for good clinical practices.[15] The design was that of a placebo run-in, double-blind, randomized crossover trial involving 40 moderately hypertensive patients. This straightforward design enabled patients not only to serve as their own controls but also to be exposed in randomized sequence to both diltiazem preparations alternately. This provided sufficient statistical power to detect differences between the two preparations with 40 patients.

After signing a written informed-consent form, completing a baseline medical history questionnaire, and receiving a physical examination, eligible patients were weaned from their existing antihypertensive medication for a 4-week single-blind placebo lead-in period. Eligibility required an age of 18 years or older with a diagnosis of uncomplicated moderate hypertension. Women of childbearing potential used medically acceptable methods of birth control and exhibited a negative pregnancy test at the start of the study. All participants were devoid of uncontrolled or unstable medical conditions that would have affected drug absorption or their ability to participate in the study.

During the last two weekly visits of the 4-week placebo lead-in period, patients with a mean seated-office diastolic blood pressure between 100 and 114 mm Hg were subjected to 24-h ambulatory blood pressure monitoring (ABPM) with a Spacelabs 90207 ABPM device. Ambulatory blood pressure was recorded at 20-min intervals between 6:00 AM and midnight and at 30-min intervals between midnight and 6:00 AM. In addition to the office blood pressure requirements, the mean daytime (8:00 AM to 4:00 PM) diastolic ambulatory blood pressure had to be > 90 mm Hg for patients to be eligible for randomization. Thus, both office and ambulatory blood pressure criteria were used to establish hypertension. Throughout the study, medication was taken at 8:00 AM ± 30 min.

TABLE 1. BASELINE AND TREATED OFFICE AND 24-H AMBU... RATE MEANS (MEAN ...

	Baseline	Single Microb...
Office		
Systolic BP (mm Hg)	153.0 ± 11.8	153.3 ± 15....
Diastolic BP (mm Hg)	103.6 ± 4.6	97.4 ±
Heart rate (bpm)	74.1 ± 8.0	73.9 ±
24-h ABPM		
Systolic BP (mm Hg)	151.7 ± 12.2	144.5 ± ...
Diastolic BP (mm Hg)	95.3 ± 8.0	89.1 ±
Heart rate (bpm)	78.0 ± 12.1	76.... ±

BP = blood pressure (mm Hg); bpm = beats per minute.

* $P < .01$ *v. baseline.*

Patients fulfilling the criteria for randomization received daily doses of 240 mg of diltiazem, delivered by either the single or the dual microbead delivery system for the first 4-week period. On the third to last day of this period, they were again subjected to ambulatory blood pressure monitoring, and on the last day of the period they were admitted to an inpatient facility for steady-state pharmacokinetic evaluations.

During the 24-h pharmacokinetic evaluation period, patients remained in a semirecumbent position and were fed three standard caffeine-free meals. On commencement of this period, an indwelling intravenous catheter and heparin lock were inserted into an antecubital vein for serial pharmacokinetic blood sampling of each patient. This occurred first at the time of dosing (8:00 AM, or time zero) and then at hourly intervals for the next 16 h. The last two samples were collected at the 20th and 24th h after dosing for a total of 19 blood samples per patient (0, 1 to 16, 20, and 24 h).

Blood sampling for pharmacokinetic analysis involved the collection of 10 mL blood into a prechilled 10-mL Vacutainer tube containing tripotassium EDTA. After mixing by several inversions, the sample was centrifuged at 3000 *g* for 5 min at 5°C. After this, 4 mL of plasma was removed from the sample with a pipet, placed in a prechilled polypropylene tube, and frozen immediately in a dry-ice isopropyl alcohol bath. The sample was immediately transported in dry ice to a −70°C freezer where it was stored in an upright position for later analysis. All plasma samples were frozen within 15 min of collection. Each polypropylene tube was labeled with only a single code number that corresponded to the patient number, study visit, and time of blood sampling. The samples were then shipped on dry ice to the Bioanalytical Laboratory at Forest Laboratories in Farmingdale, New York. Samples were analyzed by high-pressure liquid chromatography for concentrations of diltiazem, desacetyldiltiazem, and desmethyldiltiazem.

On completion of the first pharmacokinetic evaluation period, all patients had their respective study medication switched to the alternative delivery system and were ... As with the first ... to last and last ... jected to 24-h am... and 24-h pharmaco... Completion of ... study. All subj... amination, an... ment with appr...

Ambulatory ... pharmacokinet... release deliver... that differences ... by the single an... est between the ... sample sizes in ... differences in ... tween the 10th ... of 80% at a two-... .05. Of further int... reduction at the ...

TABLE 2. PHARM... 240 mg DILTIAZ... DUAL MIC...

Compound	
Diltiazem	
AUC (ng · h/...	
C_{max} (ng/mL)	
T_{max} (h)	
Desmethyldiltiazem	
AUC (ng · h/mL)	
C_{max} (ng/mL)	
T_{max} (h)	
Desacetyldil...	
AUC (ng · h/mL)	
C_{max} (ng/mL)	
T_{max} (h)	

* P < .05

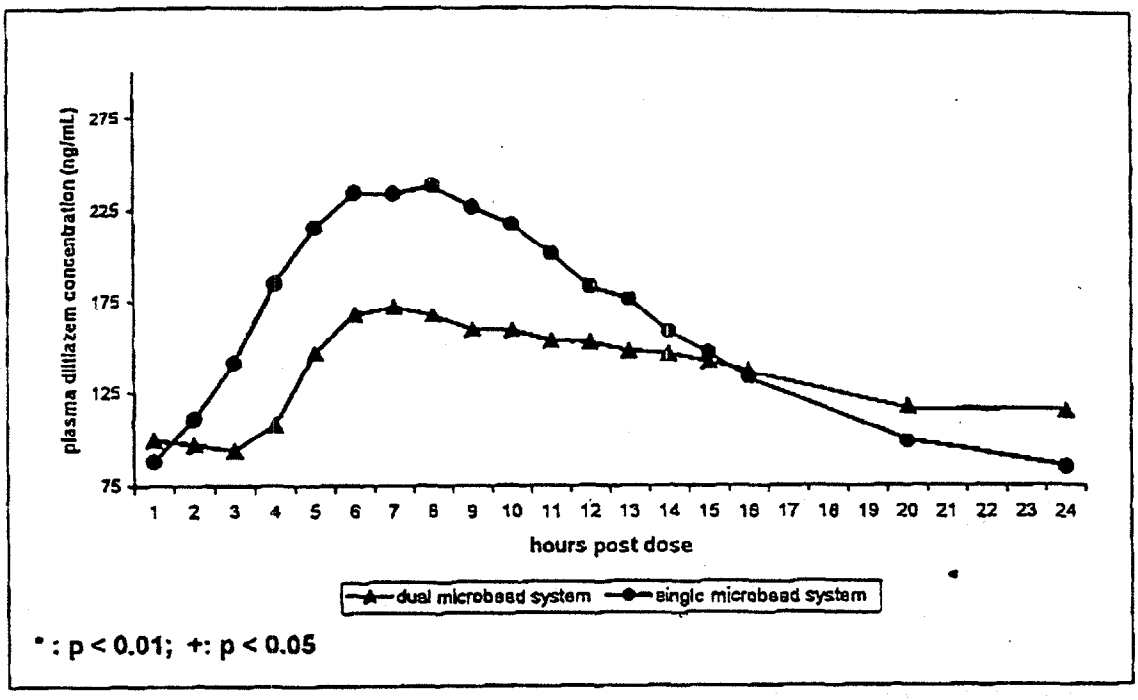

FIGURE 1. *Mean steady state plasma concentrations of 240 mg of diltiazem when delivered via single and dual microbead delivery systems.* *$P < .01$; +$P < .05$.

tion of the differences between the 24-hourly blood pressure means was also made. A priori, these differences were considered clinically meaningful when they exceeded 2 mm Hg. Additional ambulatory blood pressure monitoring endpoints included the 24-h, daytime (8:00 AM to 4:00 PM), nighttime (4:00 PM to 8:00 PM), and last 4-h (4:00 AM to 8:00 AM) means. Finally, an evaluation of ambulatory blood pressure mean differences was made for the period when plasma diltiazem concentrations between the two treatment groups differed significantly in this study.

Pharmacokinetic Evaluation The principal parameters describing the bioavailability of diltiazem and its metabolites at steady state were derived from plasma concentrations. This involved determination of the area under the curve (AUC) for plasma concentration versus time, maximum plasma concentration (C_{max}), and time of maximum plasma concentration (T_{max}). The AUC was calculated by a numerical integration, using the linear trapezoidal rule.

Adverse Events At each visit during the study the occurrence of adverse events was recorded. An adverse event was defined as any pathologic or unintended change in anatomic, physiologic, or metabolic function as indicated by changes in symptoms, physical signs, or clinical laboratory results during any phase of the clinical trial.

Statistics All data were analyzed by the statistical analysis system. Statistical procedures appropriate for crossover design were used to analyze ambulatory blood pressure monitoring parameters. Statistically significant treatment differences were set at $\alpha \leq .05$. Individual hourly blood pressure differences were regarded as clinically meaningful when they exceeded 2 mm Hg. Demographic and safety variables were analyzed statistically by one-way ANOVA, χ^2, and Fisher exact tests with a significance level set at $\alpha \leq .05$.

RESULTS

Demographics Forty patients (7 females) completed the randomized crossover phase of the study. The population consisted of 23 white, 9 black, 6 hispanic, and 2 asian people. The average age was 51.5 years. Mean height and weight were 1.75 m and 89.1 kg, respectively, resulting in a mean body surface area of 2.05 m^2.

Overall Blood Pressure Changes Table 1 shows the comparison of baseline and treatment averages for both the final office and 24-h ambulatory blood pressure. Diltiazem delivered by either system reduced the diastolic blood pressure significantly with no changes in pulse rates.

In contrast with the comparison of office blood pressure means, comparison of 24-h ambulatory blood pressure averages also detected significant systolic blood pressure reductions achieved by both delivery systems.

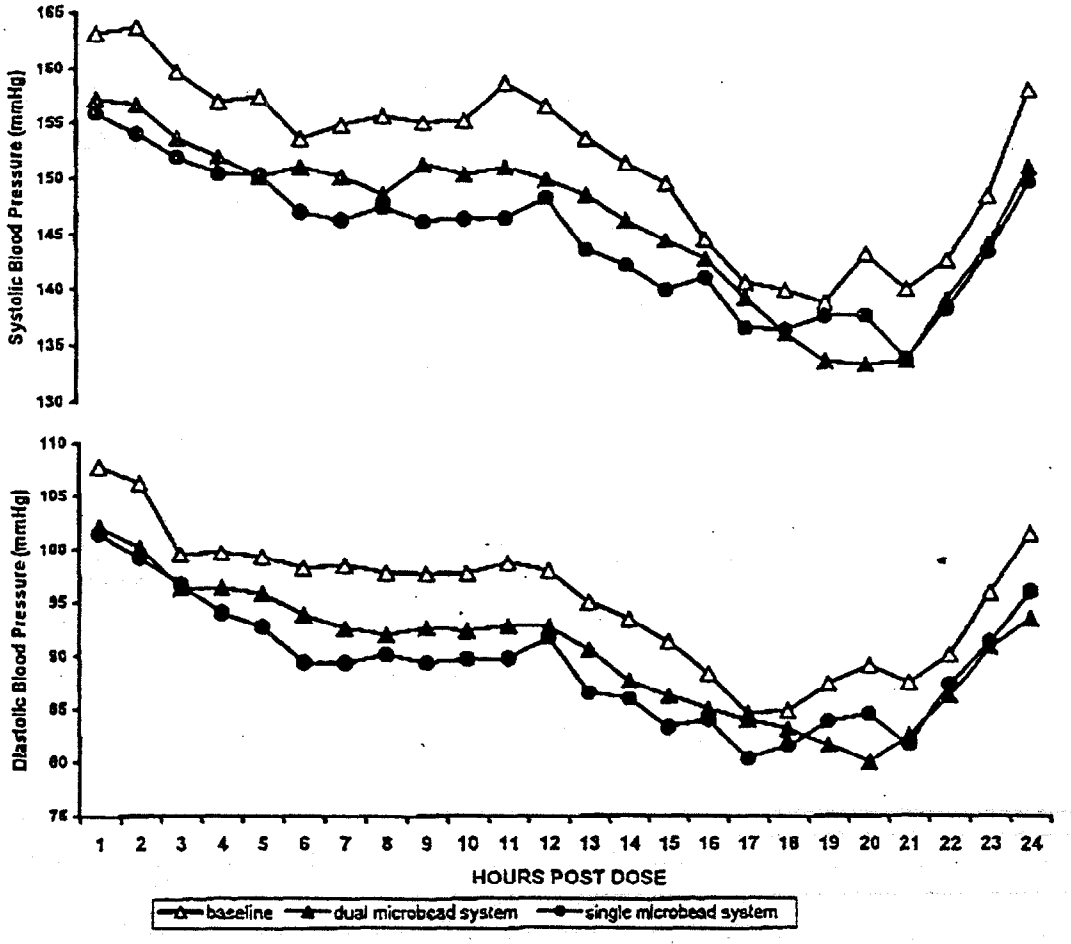

FIGURE 2. *Ambulatory blood pressure profiles at baseline and after dosing with 240 mg of diltiazem delivered via single and dual microbead delivery systems.*

Pharmacokinetic Profiles The pharmacokinetic parameters for the two delivery systems are shown in Table 2 for plasma diltiazem and its two major metabolites, desmethyldiltiazem and desacetyldiltiazem. The AUC, C_{max}, and T_{max} for diltiazem were significantly greater when delivered by the single microbead system. The AUC and C_{max} values exceeded those attained by the dual microbead system by 15% and 27.5%, respectively. Desmethyldiltiazem AUC and C_{max} produced by the single microbead system were also higher than those produced by the dual microbead system by 15% and 23.3%, respectively. No differences were noted in desacetyldiltiazem parameters.

Concentration versus time curves for plasma diltiazem are depicted in Figure 1. From the 3rd to the 13th h after dosing, the single microbead system produced significantly higher diltiazem levels (38.7%, on average) than the dual microbead system. Conversely, at 20 and 24 h after dosing, diltiazem levels achieved with the dual microbead system exceeded those of the single microbead delivery system by 27.5%.

Ambulatory Blood Pressure Profiles Systolic and diastolic 24-h ambulatory blood pressure profiles are illustrated in Figure 2. Generally, the single microbead system reduced blood pressure to a greater extent than the dual microbead system. Pulse rates were similar in both groups. However, on the basis of previous pharmacokinetic studies,[12] we focused on blood pressure differences between the 10th and 16th h after dosing as the primary endpoint of this study. Comparisons of these differences together with others during the 24-h dosing interval are shown in Table 3. For the 10th through 16th h after dosing, as well as for the midpoint of this period, the single microbead delivery system produced significantly lower systolic blood pressure than the dual microbead system (143.9 *v* 147.6 mm Hg; $P < .05$ for h 10 to 16; 143.6 *v* 149.0 mm Hg; $P < .05$ for the midpoint of this period). Similarly, diastolic blood pressure was also significantly lower at the midpoint period (86.5 *v* 99.1 mm Hg; $P < .01$). Diastolic blood pressure between the 10th and 16th h postdose also tended to be lower with the single microbead system ($P < .1$).

TABLE 3. AMBULATORY BLOOD PRESSURES FOR VARIOUS TIME PERIODS OF THE DOSING INTERVAL

	Baseline	Single Microbead System*	Dual Microbead System*
Systolic BP (mm Hg)			
10th–16th h postdose	152.7 ± 15.2	143.9 ± 13.6†	147.6 ± 12.4
10th–16th h midpoint	154.3 ± 17.0	143.6 ± 16.5†	149.0 ± 13.1
3rd–13th h postdose	156.1 ± 11.6	147.6 ± 11.9†	150.6 ± 10.3
Last 4 h	147.4 ± 15.1	141.2 ± 12.2	141.6 ± 14.7
Daytime means	157.8 ± 10.7	149.9 ± 11.7	152.3 ± 10.8
Nighttime means	148.0 ± 14.2	141.3 ± 13.3	142.8 ± 12.9
Diastolic BP (mm Hg)			
10th–16th h postdose	94.5 ± 10.4	87.2 ± 8.1‡	89.6 ± 9.2
10th–16th h midpoint	95.5 ± 11.3	86.5 ± 9.7**	91.1 ± 10.0
3rd–13th h postdose	98.1 ± 7.9	90.9 ± 8.5†	93.5 ± 8.5
Last 4 h	93.8 ± 10.3	89.1 ± 11.5	88.1 ± 9.9
Daytime means	100.5 ± 7.4	93.6 ± 8.6	95.7 ± 8.4
Nighttime means	92.1 ± 9.2	86.4 ± 8.5	87.3 ± 8.5

** Blood pressure (BP) of single and dual microbead system both significantly different from baseline.*

*† $P \leq .05$, ‡ $P \leq .1$, ** $P \leq .01$, single microbead system v dual microbead system.*

In this study, plasma diltiazem levels between the 3rd and 13th h after dosing were significantly higher with the single microbead system than with the dual system (Figure 1). During this period, both systolic and diastolic ambulatory blood pressure was significantly lower when patients received diltiazem by the single microbead system. Plasma diltiazem levels were higher with the dual microbead system at h 20 and 24 after dosing, but there were no significant differences in blood pressure between the two systems during the last 4-h period of the dosing interval (Table 3).

Pharmacokinetic and Hemodynamic Differences Differences in plasma diltiazem concentrations between the single and dual microbead systems together with the corresponding hourly differences between the blood pressure effects (compared with baseline) produced by the single and dual microbead systems are depicted in Figure 3. The single microbead system produced hourly blood pressure mean reductions from baseline that exceeded those achieved with the dual microbead system by at least 2 mm Hg for systolic blood pressure at h 2, 6, 7, 9–11, 13–15, 17, 19, and 20. A similar pattern was observed for differences between the diastolic blood pressure reductions from baseline produced by the two delivery systems. Reductions in hourly diastolic blood pressure produced by the single microbead system exceeded those produced by the dual microbead system at h 4–7, 9–11, 13, 15, and 17 after dosing; the reverse occurred at h 19, 20, and 24 after dosing. Thus, the single microbead system provides blood pressure-lowering advantages over the expanded part of the dosing interval when compared with the dual microbead delivery system: postdose h 4 to 17 versus postdose h 19, 20, and 24. However, both systems maintained antihypertensive effects throughout the dosing interval as indicated by the lower blood pressure attained during the last 4 h (Table 3).

Although the single microbead system produced higher plasma diltiazem concentrations, it did not result in an increased frequency of adverse events when compared with the dual microbead system. One or more adverse events were reported by 14 of the 40 patients. These included headache (most common), tachycardia, leg cramps, somnolence, pharyngitis, rhinitis, and urinary tract infections. These adverse events did not differ substantially when comparing the different delivery systems, and did not differ considerably from those occurring during the placebo lead-in period. The majority of adverse events were judged to be unrelated to treatment. However, four patients experienced adverse events deemed to be related to treatment. For the single microbead system, one patient had a headache and one had tachycardia; for the dual microbead system, one had a headache and one experienced insomnia. Aside from the insomnia (which was moderate in severity) all other adverse events were mild and no therapeutic actions were taken. None of the delivery systems produced an instance of hypotension and none were associated with a serious adverse event. Throughout the study, no important changes occurred in the results of electrocardiographic tracings, chemistry tests, or hematology tests. Thus, both delivery systems were equally well tolerated.

DISCUSSION

Having compared identical doses (240 mg) of diltiazem delivered to hypertensive patients by different delivery systems, this study has shown that the single microbead delivery system can impart favorable pharmacokinetic and pharmacodynamic properties to diltiazem. This could be an important finding in the use of diltiazem to treat hypertension in view of the fact

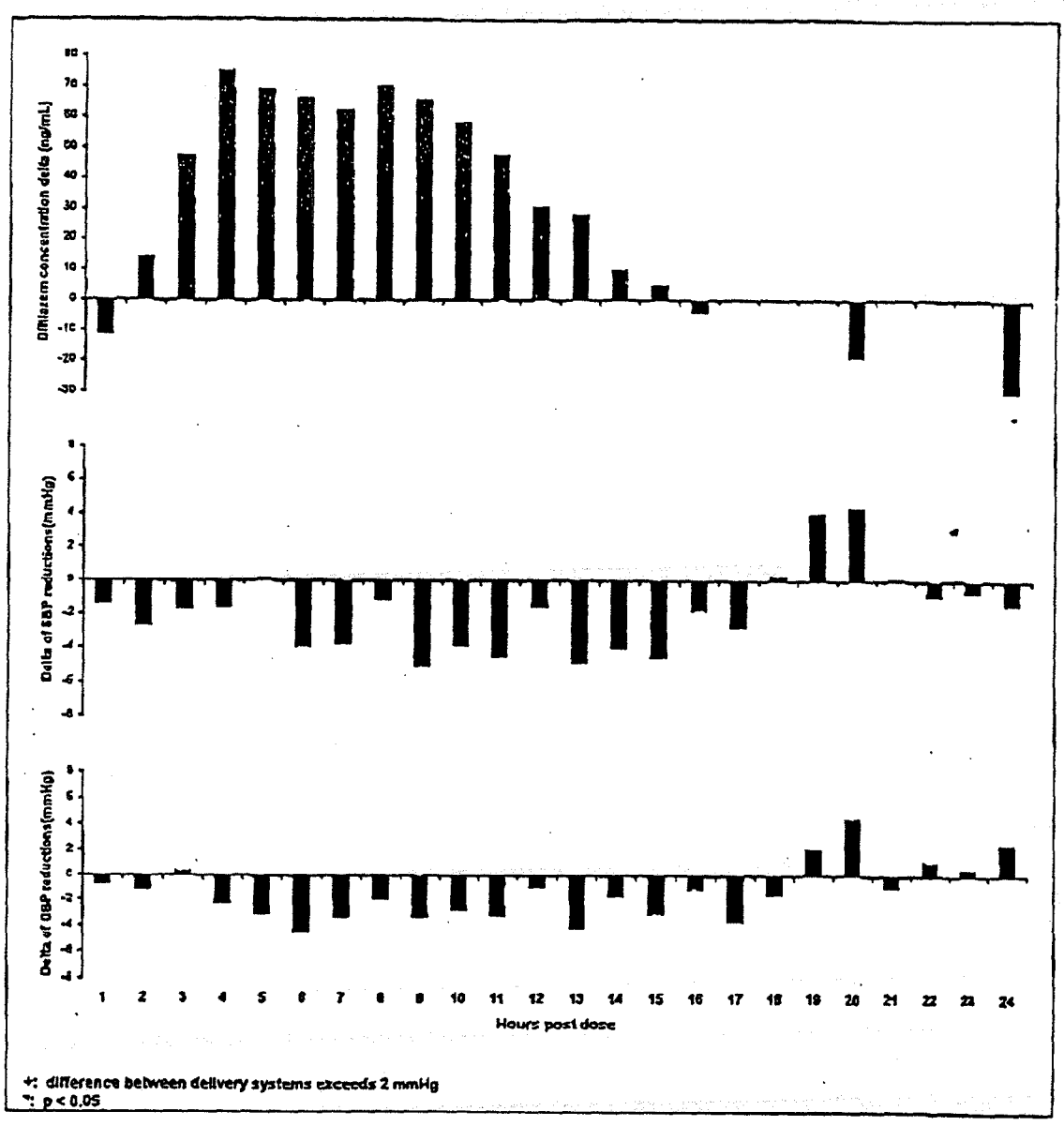

FIGURE 3. *Differences between plasma diltiazem concentrations* (Top) *and blood pressure reduction from baseline produced by the single microbead and dual microbead delivery systems. SBP = systolic blood pressure* (Center); *DBP = diastolic blood pressure* (Bottom); *Delta = differences between delivery system deltas (single bead system-dual bend system).* *$P < .05$. + *Difference between delivery systems exceeds 2 mm Hg.*

that a more intensive approach to lowering blood pressure to desired levels is advocated—especially if concomitant cardiovascular risk factors are present.[16] These data also indicate that when dosing with identical doses of diltiazem, the single microbead system produces significantly higher concentrations of diltiazem for almost half (11 of 24 h) of the once-daily dosing interval. This resulted in significantly lower systolic and diastolic blood pressure for this period of the dosing interval. Furthermore, when compared to the baseline blood pressure, blood pressure reductions achieved with the single microbead system exceeded reductions achieved with the dual microbead system by at least 2 mm Hg per hour for 10 of the 24 postdose hours. Consistent with this finding, the single microbead delivery system produced significantly higher plasma diltiazem AUC and C_{max} levels, suggesting that the single microbead system confers superior bioavailability of diltiazem compared with the dual microbead system. Also in this study, the treatment sequence changing from the single microbead system to the dual microbead system resulted in a 2.6-mm Hg increase in systolic blood pressure and a 2.1-mm Hg increase in diastolic blood pressure. Changing from the dual microbead system to the single microbead system resulted in an additional decrease of 4.5-mm Hg in

systolic blood pressure and a 2.6-mm Hg decrease in diastolic blood pressure.

This study also illustrates the pivotal role of ambulatory blood pressure monitoring in determining differing pharmacodynamic effects of antihypertensive agents. Although trough office blood pressure and simple 24-h mean blood pressure measurements were unable to distinguish between pharmacodynamic profiles of the two delivery systems an analysis of the hour-by-hour blood pressure profiles provided by ambulatory blood pressure monitoring was.

Diltiazem remains an effective agent for the treatment of hypertension.[1,2] In the Department of Veterans Affairs Cooperative study,[17,18] which assessed the efficacy of six antihypertensive agents in controlling high blood pressure in men, diltiazem had the highest success and compliance rates after 12 months of treatment. Also, this study revealed that higher doses of diltiazem (300 to 360 mg) were associated with greater blood pressure response rates than an angiotensin converting enzyme inhibitor, β-adrenergic blocker, or diuretic therapy. These doses of diltiazem are higher than the recommended once-daily starting dose of 180 or 240 mg, suggesting that initiation doses of diltiazem should be more readily uptitrated for maximum effects in hypertensive patients without underlying cardiac disease. Other studies have found a well-tolerated dose-response to 540 mg[19,20] as well as antihypertensive efficacy in severe hypertension.[21] These findings of improved blood pressure control at higher doses of diltiazem suggest that a more efficient delivery system could provide better blood pressure control at identical doses of diltiazem. Furthermore, because of differences in microbead size, the single microbead system provides a maximum per-capsule dose of 360 mg, compared with the 300 mg per capsule of the dual microbead system.

This study has demonstrated a close dependency of the hemodynamic effects of diltiazem on its plasma concentration. It has also identified pharmacokinetic and clinical disparities produced by different formulations of this antihypertensive agent. The diltiazem single microbead system appears to enhance bioavailability and efficacy.

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Dr. Janet Woodcock, Director
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
Metro Park North II – Room 150
7500 Standish Place
Rockville, MD 20855

RE: Citizen Petition Docket Number 98-0145

Dear Dr. Woodcock:

This letter is being provided in support of the Citizen Petition of Andrx Pharmaceuticals, Inc. regarding the need for further agency consideration of the requirements for controlled-release diltiazem products.

As one of the original preclinical and clinical investigators on diltiazem back in the late 70s and early 80s, it became clear that specific formulations can affect the delivery of the active molecule differently. We first noted a dose dependency in absorption in 1982 prior to the development of any of the sustained-release diltiazem products. Subsequently, three products were developed, all of which utilized a different delivery mechanism. Similarly, and for good reason, all of these products were listed as "BC" products by the FDA. This differentiation in therapeutic response associated with different formulations can have clinical impact, as noted in the February, 1994 Board of Pharmacy newsletter from the state of South Carolina. In this situation, renal transplant patients that were receiving a sustained-release diltiazem formulation to both prevent renal toxicity and raise cyclosporin levels, received a substitute formulation. Following the "generic substitution," four of these patients ended up back in the hospital and had to be retitrated. This situation provides a clear example of what can happen when one sustained-release diltiazem formulation is substituted for another.

In reviewing this bioavailability data, I would also encourage you to look at the number of patients that have their serum levels drop below 40-50 nanograms/ml during the 24 hours following dose. When I stipulated 40 nanogram/ml as the minimal effective concentration and evaluated bioavailability studies, I found a significant difference in the number of patients who were able to stay above that

therapeutic level with the different "BC"-rated formulations that are currently available. In my experience, this therapeutic MEC provides a reasonable rule of thumb for patient response. Thus, for a formulation to be considered equivalent, it should maintain serum levels in this range over 24 hours as compared to the reference standard.

In summary, in the same manner in which the FDA considers Tiazac and Cardizem-CD to not be therapeutically equivalent, a "one-peak" diltiazem formulation should not be considered therapeutically equivalent to a "two-peak" formulation.

Sincerely,

Robert W. Piepho, Ph.D., FCP
Dean and Professor